

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/130392/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Sullivan, Patrick F. and Owen, Michael J. 2020. Increasing the clinical psychiatric knowledge base about pathogenic copy number variation. *American Journal of Psychiatry* 177 (3) , pp. 204-209. 10.1176/appi.ajp.2019.19040335

Publishers page: <http://dx.doi.org/10.1176/appi.ajp.2019.19040335>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



Increasing the Clinical Psychiatric Knowledge Base about Pathogenic Copy Number Variation

Patrick F Sullivan MD FRANZCP^{1,2}, Michael J Owen MBChB, PhD, FRCPsych³

¹ University of North Carolina, Departments of Genetic and Psychiatry, Chapel Hill, NC, US

² Karolinska Institutet, Department of Medical Epidemiology and Biostatistics, Stockholm, Sweden

³ Cardiff University, MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff, Wales, UK

Correspond with PF Sullivan (pfsulliv@med.unc.edu) and MJ Owen (owenmj@cardiff.ac.uk).

Plain language summary: Copy number variants – increases or decreases in the inherited “dosages” or one or more important genes – are increasingly recognized in clinical psychiatry. We call for a clinical crowd-sourcing, for more systematic case reports to help clinicians identify sound treatment options.

Abstract: Specific copy number variants (CNVs) have been robustly associated with intellectual disability, autism, and schizophrenia. Most of the literature focus has been on documenting the existence of these phenomena. There are few data to guide therapeutic choices for these “orphan” diseases. We call for systematic and longitudinal case reports which, if carefully conducted, may provide crucial initial knowledge to guide therapeutics. We provide a step-by-step overview, a tailored set of consensus criteria for high-quality case reports, and a specific set of learning resources.

Imagine an initial psychiatric interview that begins with the chief complaint, “I have a *de novo* 16p11 duplication and they say I have schizophrenia and Asperger’s. What does this mean for me and my family? How can you help me?” Provided that the patient’s report can be verified, this chief complaint has a strong scientific empirical basis. As the patient says, this “copy number variant” or CNV results in changes in the number of copies of ~30 genes located on a 600,000 base pair region on the short arm of chromosome 16, and this rare genetic mutation increases risk for autism and schizophrenia (**Supplemental Note 1**). How exactly would you help? What evidence would support your clinical choices? On the basis of current knowledge, a clinician should explore the possibility of other psychiatric diagnoses (e.g., major depression and speech and language delay) and be alert for the presence of physical abnormalities including renal and urinary malformations as well as consider the need for genetic counseling. However, while there may be broader implications for the patient and their family, to the best of our knowledge, there are few relevant data that inform the psychiatric management of this patient. Thus, how can our field cooperate in order to rapidly increase knowledge relevant to clinical management?

Although this scenario might seem far-fetched, genetic evaluations are increasingly part of standard-of-care in psychiatry. A “genetic workup” is increasingly part of the clinical evaluation of children with moderate/severe intellectual disability, marked developmental delay, and autism, and is justifiable for adults who present similarly or who have complex presentation (see below). In fact, psychiatrists who treat individual with severe psychiatric disorders (including ourselves) are certain to have encountered patients with important genetic changes – and we probably did not know it. The rapid pace of progress in medical genomics means that these topics and their implications will be unfamiliar to many clinicians, and a number of educational resources are available (**Table S1**).

Normally, children inherit a paternal and a maternal copy of every autosome (chromosomes 1-22). Occasionally, there are errors in the meiotic or mitotic machinery so that large regions, often containing

multiple genes, are lost or gained. Such changes are termed CNVs. These can occur at the level of a whole chromosome (e.g., trisomy 21, 48.1 megabases) or at finer levels (hundreds of kilobases or smaller as with the 16p11 CNV). Many pathogenic CNVs recur due to regional genomic features and can be found worldwide (1). Genomic studies have established the etiological importance of specific CNVs for psychiatric outcomes, with most of these CNVs associated with variable outcomes (pleiotropy) including moderate/severe intellectual disability, developmental delay, autism, tics, dyscoordination, and schizophrenia (*Figure 1a*).

In samples seen in clinical psychiatry, current estimates suggest that a clinically- or etiologically-relevant CNV is likely to be present in around 2-3% of people with schizophrenia, 10% of people with autism, and 25% or more of people with intellectual disability (2-4). In general, the greater the severity, the higher the prevalence (i.e., lesser in unselected population surveys and higher in the most severely ill).

The accumulation of disease-relevant genomic data begs the question of how this should impact on clinical decision-making but the clinical knowledge base is limited. We need more treatment and management data to guide therapeutic choices for people with a pathogenic CNV and a severe psychiatric disorder, and to be able to address questions about familial risk. Although the associations of specific CNVs as etiological risk factors are secure, we do not now have an adequate knowledge base to inform the practice of clinical psychiatry. *Figure 1b* summarizes the content of the case report literature for two prominent CNVs, 22q11del and 16p11del/dup. For both, the emphasis is on diagnostic features, unusual presentations, and information particularly salient to clinical geneticists, neurologists, and pediatricians. In reviewing the literature in more detail, we found that the clinical knowledge base is very sparse – there are few data relevant to the question in the first paragraph: “how can you help me?”

Although, as a group, these CNVs are a not uncommon etiological risk factor, the individual CNVs are rare and almost all are “orphan diseases” (i.e., impacting under 200,000 people in the US, lifetime prevalence < 0.06%; *Supplemental Note 2*). Accruing sizable samples for systematic study requires international consortia, considerable expense, and many years of effort. A prime example is the International 22q11.2 Deletion Syndrome (22q11DS) Brain Behavior Consortium (5). This consortium has assembled a sample of 1,616 psychiatrically well-characterized cases and obtained genomic data on >300 adults split evenly into those with schizophrenia and those without. The aims of this study are to understand how other genetic and non-genetic factors influence the expression of schizophrenia that may be of wider relevance to the general population, and to provide information on the precursors and antecedents of schizophrenia and to serve as a base for future longitudinal studies aiming to study the neurodevelopmental trajectories of deletion carriers. The outcomes of the study are beginning to appear and include the largest characterization of psychiatric outcomes in 22q11DS to date, and identification of childhood antecedents of psychotic outcomes (6, 7).

It is reasonable to ask whether improved therapeutics are likely. We do not know. However, as a proof-of-concept, Deborah Levy and colleagues recently reported two individuals with psychotic disorders and very rare CNV triplications of the glycine decarboxylase gene (8). Under the assumption of NMDA hypofunction due to increased glycine catabolism (and low levels of brain glycine and D-serine), they demonstrated clinical improvement in psychotic and mood symptoms with oral glycine supplementation (double-blind, placebo-controlled). If a clinician were to encounter a patient with this CNV in the future, this report would provide reasonable therapeutic guidance.

We propose a systematic effort to obtain clinical data useful to management in clinical psychiatry. We effectively propose “clinical crowd-sourcing” that combines the advantages of a distributed effort with a comprehensive and systematic structure in order to yield high-quality case-report and case series knowledge to inform clinical psychiatric management. Our proposal has the following steps:

(1) Detection. We need to test more patients for CNVs. In fact, there is a strong case for universal testing for some psychiatric disorders, particularly early-onset and severely impairing conditions (moderate/severe intellectual disability and autism) as well as chronic psychotic disorders in adults. A positive result is relevant to clinical management – most large CNVs are multisystem disorders with increased risk of cardiac, neurological, endocrine, renal, hematological, and digestive complications (9). We encountered a patient whose idiopathic thrombocytopenia was chased after for years but was almost certainly a consequence of 22q11DS (10). We know of drug companies working on therapeutics for specific CNVs; if targeted medications become available in the future, we need to know the patients for whom these therapies may be indicated. The presence of a CNV can be relevant to reproductive planning, but the wide range of psychiatric and cognitive outcomes and incomplete penetrance calls for nuanced and informed genetic counseling (11).

CNV testing is typically offered for children with ID, developmental delay or neurodevelopmental disorders. But CNVs are also risk factors for adult psychiatric cases particularly schizophrenia. What clinical features increase the likelihood of the presence of a CNV and should act as “flags” for targeted testing in adult psychiatry? We are not aware of systematic studies and there is clearly a pressing need for these as we argue below. However, based on current knowledge, we would highlight premorbid low intelligence, a history of childhood onset neurodevelopmental disorder, congenital malformations, dysmorphic features, and developmental delay (missing developmental milestones). A family history of schizophrenia or other neurodevelopmental disorders may also be relevant (although pathogenic CNVs frequently occur *de novo* and so a family history in a parent is often absent). Finally, we never discount the importance of the intuition of experienced clinicians, or the sense that a particular patient is distinctively different from others in the same diagnostic category. Examples here include very severe symptoms or extreme treatment refractoriness, and prominent physical co-morbidity.

Exactly what test to order depends on the clinical context and on the availability and cost of technologies. We offer the following general considerations. First, consultation with a clinical geneticists and/or a genetic counsellor may be helpful. Second, for adult psychotic disorders, evaluation of CNVs would be a typical starting point. One technology for this purpose are chromosomal microarrays (CMA) which can identify the presence of large pathogenic CNVs (cost approximately \$US 300). Third, for early onset, severe psychiatric disorders, a typical panel would include CMA and resequencing of the protein-coding portion of the genome (whole exome sequencing) or whole genome sequencing. Applying the same technologies to both biological parents can help in prioritizing detected variants and in determining whether a variant is *de novo* or inherited.

(2) Capture the needed data. In most instances, case reports that only describe the co-occurrence of a known CNV with a psychiatric disorder may not be particularly notable for associations that have been extensively documented. At the same time, there may be some novel or remarkable feature that would support publication (e.g., our report of a man with 22q11DS and Huntington’s Disease (10)).

In our opinion, we need case reports and case series that have two key features: (a) comprehensive initial assessment and (b) systematic description of longitudinal course and the impact of therapeutic efforts.

Initial assessment should include a multi-informant history of salient events in pregnancy, birth, childhood development, adolescence, and adulthood. Assessments or indications of intellectual function across development are very important (if not essential). Collecting such data from a psychiatric perspective is generally routine in clinical practice. However, for CNVs, there should be particularly attention to congenital and multi-system abnormalities across all organ systems. The presence of physical comorbidities should be sought, perhaps in collaboration with medical colleagues from other relevant specialties, bearing in mind those conditions known to be associated with a specific CNV.

Finally, a thorough family history should be obtained with a focus on the range of neurodevelopmental disorders including schizophrenia that are associated with risk CNVs. Many would suggest that brain imaging using MRI is important.

The critical missing ingredient is the longitudinal course and impact of therapeutics. There needs to be a systematic description of age-dated therapeutics across all modalities (pharmacological as well as behavioral and psychological). These need also be connected to age-dated assessments of functional capacity, occupation, role function, and inpatient, emergency, and outpatient treatment. Combining these data are needed to establish correlations as to what therapeutic strategies were optimal for this particular patient. In effect, a variant on the “N-of-one” clinical study.

We note that modern data science (12) has many excellent and free tools for obtaining, refining, summarizing, and presenting complex longitudinal data. This is increasing easy to accomplish given the availability of electronic medical records. For example, [Figure 1c](#) took 5 minutes to make but captures 25 years of pharmacotherapy for a person with highly treatment-resistant psychosis.

(3) Publish a case report. It is then important to let the scientific community know what you have learned. The particular focus should be on what worked, what did not work, and what you might do differently if you could do it over. We strongly advocate for following explicit guidelines for the structure and content of a case report – for instance the CARE criteria, which were developed in the general medical context to improve completeness and transparency and facilitate the systematic aggregation of information across reports (13) ([Table S3](#)). In particular, the title should include “case report” and standard terms for the specific genetic change and the psychiatric diagnosis. Reasonable examples of CNV case reports/series may be found in these references (10, 14). There are multiple target journals for these case reports. Particularly detailed or notable case reports may appear in higher profile journals; however, it is critical for these case reports to be findable via inclusion in searchable resources like PubMed and PubMed Central. There are multiple open-access journals devoted to case reports and indexed in PubMed. A basic web search for “case report journals” found 10, and there are even overviews on the choice of case report journal (15).

(4) Benefits and challenges. The potential benefits of what we propose are to allow other clinicians to benefit from the experiences of colleagues in the struggle to deliver effective clinical management and identify treatment options for individuals with rare pathogenic CNVs and severe mental illness. Many patients with CNVs experience protracted and stressful “diagnostic odysseys” in referrals to multiple specialists for organ-specific evaluations when, in the end, the root cause is a CNV with impacts on multiple systems. Minimizing time to CNV identification would minimize such odysseys and rapidly signpost potentially appropriate non-psychiatric assessments. Moreover, it is possible that detailed evaluation of these rare patients could yield therapeutic and etiological ideas relevant to patients with idiopathic forms of these disorders.

“Bespoke therapeutics” may ultimately be an important benefit. For certain rare CNVs, the literature may suggest a therapy that is uniquely tailored to an individual with a particular CNV. Current examples include the use of oral glycine in CNV triplications of the glycine decarboxylase gene (8), and the anecdotal use of oral magnesium supplementation in Burnside-Butler syndrome (a 15q11.2 CNV deletion that impacts *NIPA1* and *NIPA2* which are involved in brain magnesium transport) (16). We contend that by rapidly sharing and disseminating clinical and therapeutic findings, we may be able to build on these small but important beginnings.

A focus on copy number variation can also improve diagnostic classification. Many CNVs have highly variable clinical presentations that can include combinations of intellectual disability, specific learning impairments, autism, ADHD, anxiety/mood disorders, and psychotic disorders. In current diagnostic

schemas, these are coded according to the clinical presentation; however, while this has value, it is crudely akin to coding rash, fever, headache, photophobia, and altered mental status instead of *N. meningitidis* meningitis. Given the range psychiatric disorders and medical comorbidities associated with these CNVs, a primary diagnosis that includes reference to the CNV may be more parsimonious and to capture and to alert clinicians to the full range of important sequelae.

Several challenges are noted above, particularly the greater need for longitudinal and process outcome data (as opposed to merely documenting the co-occurrence of a CNV and a clinical presentation). An additional challenge is that advances in psychiatric and medical genetics mean that psychiatrists (particularly those in training) will need to understand how to generate, interpret, and explain genetic findings to their patients as well as how to use these data clinically (17). There are multiple ways to obtain direct-to-consumer genomics (many of dubious clinical utility), and clinicians will increasingly be faced with questions about their relevance. For interested readers, [Table S1](#) contains a list of learning resources. There is clearly a need to embed genetics training deeply in residency training programs and to upskill practicing psychiatrists. Nurnberger et al. provide recommendations for psychiatry residency training and note “the basic principles of genetics...are essential to current psychiatric patient care” (18).

A key challenge is clinical synthesis: e.g., for the patient introduced at the start of this article, how would a clinician efficiently, effectively, and accurately extract clinical guidance from the literature? Literature reviews are usually a great starting point (if they exist but with the caveat that they miss case reports since submission). Moreover, they may not cover the exact clinical need. We suggest there is an unmet need: we need a structured and curated on-line database that captures case report data at the interface of genetics and clinical psychiatry. This is largely informatics, but requires a funder to champion and support the idea. The idea is straightforward: to systematically capture the genetic mutation, the clinical phenotypes using a structured vocabulary (e.g., the Human Phenotype Ontology), therapeutics attempted, and therapeutic outcomes and adverse events. A reasonable model for this is the DECIPHER database in the UK (<https://decipher.sanger.ac.uk>). In addition, such a database could serve as the basis for research and grant applications to derive clinical and biological hypotheses as well as to support accrual of “orphan” patients for future systematic studies.

The existence of a sizable body of cases reports – particularly if prepared to a high standard – would provide practical guidance for the clinical psychiatric management of people with a psychiatric disorder and a pathogenic CNV. If we were to have ten such reports for the vignette at the start of this essay (for a *de novo* 16p11 CNV, schizophrenia, and Asperger’s, “how can you help me?”), you could synthesize the reports to derive an empirical management plan. You might also discover a psychiatric colleague with particular expertise in treating people with 16p11 CNVs in adult patients and a conversation or email exchange could be helpful.

Better case report data are literally better than nothing. However, ultimately, there is a need for more adequately powered studies that are able to relate specific genomic risk factors to clinical and neurocognitive outcomes and therapeutics. The individual CNVs are rare but the clinical psychiatric phenotypes with which they are associated are not, and the variable expressivity and pleiotropy seen offer an important opportunity to investigate the role of other genetic and environmental factors in modifying psychiatric outcomes and to deliver findings of relevance to psychiatric disorders more generally. They also offer an opportunity for studying groups of subjects in early childhood at high risk of later childhood and adult disorders and of studying the developmental course of psychiatric disorders and identifying potentially modifiable antecedents and modifiers. It is gratifying that NIMH has identified the potential of these studies and the need to assemble coordinated multidisciplinary and multi-site teams capable of combining genomic data with comprehensive dimensional and categorical

phenotype data. This is an excellent beginning but we believe that more attention/funding to this emerging area is required.

Figure legends

Figure 1a: CNVs associated with intellectual disability, developmental delay, autism, and/or schizophrenia (2, 19-21). Shown are ideograms of chr1-chr22, chrX, and chrY (hg19 coordinate system). The raw data are in **Table S2**. These 122 CNVs were merged into 57 regions for display (collapsing across sources, condition, and deletion/duplication status). The blue blocks show the location of CNVs association with intellectual disability, developmental delay, autism, and/or schizophrenia. These regions comprise 142.1 megabases or about 4.6% of the genome.

Figure 1b: Word clouds of titles and abstracts from PubMed searches for case reports for 22q11 (left) and 16p11 (right). Font size and coloration indicate word frequency. These word clouds and more detailed inspection of the primary citations reveal little information to guide psychiatric therapeutics.

Figure 1c: Illustration of graphical methods to succinctly portray a complex pattern of pharmacotherapy over 25 years. Using an electronic pharmacy record, the dosage of each psychiatric medicine per week was tabulated. The X-axis is age with each year comprising up to 52 thin, weekly slices. The Y-axis shows broad drug classes and the vertical sections within each class show the specific medications. The color of each vertical slice depicts the ratio of the prescribed amount of drug to “defined daily dose” specified by the World Health Organization for each drug (from very light to very dark red with the two darkest colors showing a ratio over 1). This person has received substantial trials of four typical antipsychotics and significant trials of four atypical antipsychotics (including around a year of clozapine). There were also extensive trials of valproate, lithium, and lorazepam. Adding measures of symptoms and function could allow clinical correlations of clinical efficacy.

Competing Financial Interests

PFS reports the following potentially competing financial interests in the past 3 years: Lundbeck (advisory committee, grant recipient), Pfizer (Scientific Advisory Board), and Element Genomics (consultation fee). MJO is a grant recipient from Takeda Pharmaceutical Company.

Acknowledgements & Funding

PFS acknowledges support from the Swedish Research Council (Vetenskapsrådet, award D0886501 and the US National Institute of Mental Health (MH077139 and MH1095320). MJO acknowledges support from a Wellcome Trust Strategic Award (100202/Z/12/Z), a Medical Research Council Centre Grant (G0801418), and program grant (G0800509). PFS and MO acknowledge support of the COSYN project by the Horizon 2020 Program of the European Union (RIA grant agreement n° 610307). We are indebted to Drs. Rick Josiassen, Maya Lichtenstein, Marty Farrell, and Robert Stowe for helpful discussions.

References

1. Kirov G, Rees E, Walters JT. What a psychiatrist needs to know about copy number variants. *BJPsych Advances*. 2015;21:157-163.
2. Rees E, Kendall K, Pardiñas AF, Legge SE, Pocklington A, Escott-Price V, MacCabe JH, Collier DA, Holmans P, O'Donovan MC, Owen MJ, Walters JT, Kirov G. Analysis of Intellectual Disability Copy Number Variants for Association With Schizophrenia. *JAMA Psychiatry*, 2016: 73:963-969.

3. Schaefer GB, Mendelsohn NJ, Professional P, Guidelines C. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. *Genet Med*. 2013;15:399-407.
4. Kessi M, Xiong J, Wu L, Yang L, He F, Chen C, Pang N, Duan H, Zhang W, Arafat A, Yin F, Peng J. Rare Copy Number Variations and Predictors in Children With Intellectual Disability and Epilepsy. *Front Neurol*. 2018;9:947.
5. Gur RE, Bassett AS, McDonald-McGinn DM, Bearden CE, Chow E, Emanuel BS, Owen M, Swillen A, Van den Bree M, Vermeesch J, Vorstman JAS, Warren S, Lehner T, Morrow B. A neurogenetic model for the study of schizophrenia spectrum disorders: the International 22q11.2 Deletion Syndrome Brain Behavior Consortium. *Mol Psychiatry*. 2017;22:1664-1672.
6. Schneider M, Debbane M, Bassett AS, Chow EW, Fung WL, van den Bree M, Owen M, Murphy KC, Niarchou M, Kates WR, Antshel KM, Fremont W, McDonald-McGinn DM, Gur RE, Zackai EH, Vorstman J, Duijff SN, Klaassen PW, Swillen A, Gothelf D, Green T, Weizman A, Van Amelsvoort T, Evers L, Boot E, Shashi V, Hooper SR, Bearden CE, Jalbrzikowski M, Armando M, Vicari S, Murphy DG, Ousley O, Campbell LE, Simon TJ, Eliez S, International Consortium on B, Behavior in 22q11.2 Deletion S. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. *Am J Psychiatry*. 2014;171:627-639.
7. Niarchou M, Chawner S, Fiksinski A, Vorstman JAS, Maeder J, Schneider M, Eliez S, Armando M, Pontillo M, Vicari S, McDonald-McGinn DM, Emanuel BS, Zackai EH, Bearden CE, Shashi V, Hooper SR, Owen MJ, Gur RE, Wray NR, van den Bree MBM, Thapar A, International 22q11.2 Deletion Syndrome B, Behavior C. Attention deficit hyperactivity disorder symptoms as antecedents of later psychotic outcomes in 22q11.2 deletion syndrome. *Schizophr Res*. 2019;204:320-325.
8. Bodkin JA, Coleman MJ, Godfrey LJ, Carvalho CMB, Morgan CJ, Suckow RF, Anderson T, Ongur D, Kaufman MJ, Lewandowski KE, Siegel AJ, Waldstreicher E, Grochowski CM, Javitt DC, Rujescu D, Hebring SJ, Weinshilboum R, Burgos-Rodriguez S, Kirchhoff C, Visscher T, Vuckovic A, Fialkowski A, McCarthy S, Malholtra D, Sebat J, Goff DC, Hudson JI, Lupski JR, Coyle JT, Rudolph R, Levy DL. Targeted Treatment of Individuals with Psychosis Carrying a Copy Number Variant Containing a Genomic Triplication of the Glycine Decarboxylase Gene. *Biol Psychiatry*. 2019.
9. Crawford K, Bracher-Smith M, Owen D, Kendall KM, Rees E, Pardinas AF, Einon M, Escott-Price V, Walters JTR, O'Donovan MC, Owen MJ, Kirov G. Medical consequences of pathogenic CNVs in adults: analysis of the UK Biobank. *J Med Genet*. 2019;56:131-138.
10. Farrell M, Lichtenstein M, Crowley JJ, Filmyer DM, Lazaro-Munoz G, Shaughnessy RA, Mackenzie IR, Hirsch-Reinshagen V, Stowe R, Evans JP, Berg JS, Szatkiewicz J, Josiassen RC, Sullivan PF. Developmental Delay, Treatment-Resistant Psychosis, and Early-Onset Dementia in a Man With 22q11 Deletion Syndrome and Huntington's Disease. *Am J Psychiatry*. 2018;175:400-407.
11. Olsen L, Sparso T, Weinsheimer SM, Dos Santos MBQ, Mazin W, Rosengren A, Sanchez XC, Hoeffding LK, Schmock H, Baekvad-Hansen M, Bybjerg-Grauholm J, Daly MJ, Neale BM, Pedersen MG, Agerbo E, Mors O, Borglum A, Nordentoft M, Hougaard DM, Mortensen PB, Geschwind DH, Pedersen C, Thompson WK, Werge T. Prevalence of rearrangements in the 22q11.2 region and population-based risk of neuropsychiatric and developmental disorders in a Danish population: a case-cohort study. *Lancet Psychiatry*. 2018;5:573-580.
12. Grolemond G, Wickham H: R for Data Science. Sebastapol, CA, O'Reilly Media, Inc.; 2016.
13. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D, Group C. The CARE guidelines: consensus-based clinical case reporting guideline development. *BMJ Case Rep*. 2013;2013.

14. Bouwkamp CG, Kievit AJA, Markx S, Friedman JI, van Zutven L, van Minkelen R, Vrijenhoek T, Xu B, Sterrenburg-van de Nieuwegiessen I, Veltman JA, Bonifati V, Kushner SA. Copy Number Variation in Syndromic Forms of Psychiatric Illness: The Emerging Value of Clinical Genetic Testing in Psychiatry. *Am J Psychiatry*. 2017;174:1036-1050.
15. Rison RA, Shepphird JK, Kidd MR. How to choose the best journal for your case report. *J Med Case Rep*. 2017;11:198.
16. Butler MG. Magnesium Supplement and the 15q11.2 BP1–BP2 Microdeletion (Burnside–Butler) Syndrome: A Potential Treatment? *International Journal of Molecular Sciences*. 2019.
17. Besterman AD, Moreno-De-Luca D, Nurnberger JI, Jr. 21st-Century Genetics in Psychiatric Residency Training: How Do We Get There? *JAMA Psychiatry*. 2019.
18. Nurnberger JI, Jr., Austin J, Berrettini WH, Besterman AD, DeLisi LE, Grice DE, Kennedy JL, Moreno-De-Luca D, Potash JB, Ross DA, Schulze TG, Zai G. What Should a Psychiatrist Know About Genetics? Review and Recommendations From the Residency Education Committee of the International Society of Psychiatric Genetics. *J Clin Psychiatry*. 2018;80.
19. Cooper GM, Coe BP, Girirajan S, Rosenfeld JA, Vu TH, Baker C, Williams C, Stalker H, Hamid R, Hannig V, Abdel-Hamid H, Bader P, McCracken E, Niyazov D, Leppig K, Thiese H, Hummel M, Alexander N, Gorski J, Kussmann J, Shashi V, Johnson K, Rehder C, Ballif BC, Shaffer LG, Eichler EE. A copy number variation morbidity map of developmental delay. *Nature genetics*. 2011;43:838-846.
20. Stefansson H, Meyer-Lindenberg A, Steinberg S, Magnusdottir B, Morgen K, Arnarsdottir S, Bjornsdottir G, Walters GB, Jonsdottir GA, Doyle OM, Tost H, Grimm O, Kristjansdottir S, Snorrason H, Davidsdottir SR, Gudmundsson LJ, Jonsson GF, Stefansdottir B, Helgadottir I, Haraldsson M, Jonsdottir B, Thygesen JH, Schwarz AJ, Didriksen M, Stensbol TB, Brammer M, Kapur S, Halldorsson JG, Hreidarsson S, Saemundsen E, Sigurdsson E, Stefansson K. CNVs conferring risk of autism or schizophrenia affect cognition in controls. *Nature*. 2014;505:361-366.
21. Deciphering Developmental Disorders Study. Large-scale discovery of novel genetic causes of developmental disorders. *Nature*. 2015;519:223-228.